UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,996	02/08/2002	Ruiping Liu	MEMORY-2	9946

24980 7590 07/11/2006

MILLEN, WHITE, ZELANO & BRANIGAN, PC
2200 CLARENDON BLVD
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,996	LIU ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-36,60,61,68,70-75,77,78,80 and 83-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-36,60,61,68,70-73,75,78,80 and 83-94* is/are rejected.

7)☒ Claim(s) *74 and 77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-4, 6, 10, 16-17, 21, 27-32 and 60-61, 68, 70, 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley(1990) i.e. Reference 4 of 11/6/2002 submission or Reference A34 of the 4/15/2002 IDS.

Compound 2 is an antiviral against rhinovirus type 1B. The species is excluded by proviso, but this methyl compound is a homolog of the corresponding ethyl compound, i.e. compound where R1 in the claims is ethyl. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl

groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 247; *Ex parte Henkel*, 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *In re Herr*, 134 USPQ 176; *Ex parte Dibella*, 157 USPQ 59; *In re Zickendraht*, 138 USPQ 22; *Ex Parte Fischer*, 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39; *In re Bowers and Orr*, 149 USPQ 570.In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." See also MPEP 2144.09, second paragraph. Note that Rhinovirus always causes inflammation.

Species 11, 8, 9, 12, 14, 15, 17, 18, 21 and 22., having the cyclopropyl and 9-methyl benzyl, no longer renders the claim 1 (or claim 98) obvious because of the expanded (b) proviso. These species would still be relevant to claim 68 and 70 because the amendments

to the claim 68 provisos are not relevant to this species, and the claim 70 provisos were not amended.

The traverse is unpersuasive. With regard to compound 2, the remarks state, "In the numerous cases cited by the Examiner, the compounds involved differed by one or two methyl groups wherein the alkyl groups in question were substituents attached to a carbon ring atom or a carbon atom of a chain." Exactly that situation applies here, for the "or a carbon atom of a chain" branch of the above sentence. The carbon chain of methyl has an additional methyl group attached to extend the chain from methyl to ethyl. It is not seen what difference it makes what the entire chain is ultimately attached to. In every one of the cases cited, the extra methyl group is attached to something different. Each case has its own structure. However, the concept of a homolog is independent of what the alkyl chain is ultimately connected to. Applicants have not presented any definition of homolog that makes it dependent on what the alkyl chain is attached to.

Claims 1, 3, 6, 10, 16-17, 21, 27-32, 35, 60-61, 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bourguignon i.e. Reference 5 of 11/6/2002 submission or Reference A37 of the 4/15/2002 IDS.

Compound 6i corresponds to R2=benzyl, R1=H, and is excluded by proviso. Even with the rewritten third proviso, the compound is still a homolog. However, it renders the corresponding homolog where R2= dimethyl-benzyl obvious, for reasons set forth previously. The two methyl groups could be on the alpha-carbon, one on the alpha and one on the ring, or both on the ring. It also renders obvious the chain homolog where R2 is phenethyl, i.e. $(CH_2)_3$-Phenyl rather than $(CH_2)_1$-Phenyl (note that while $(CH_2)_2$-Phenyl was excluded, $(CH_2)_3$-Phenyl was not). The traverse on the chain homolog issue is not

persuasive. *Ex parte Ruddy*, 121 USPQ 427 specifically has an extra has a C_2H_4 link between a phenyl ring and a heterocyclic ring, exactly as here in the $(CH_2)_3$-Phenyl situation.

Compound 6d, 6k, and 6l no longer render obvious the claims because of the expanded first proviso.

Claims 1, 4, 27-29, 60, 94 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley(1997) i.e. Reference A38 of the 4/15/2002 IDS.

The compounds are antipsychotic agents. Compound 80 (see table 7) corresponds to R1=cyclopropyl, R2= -(CH_2)-cyclopropyl. This species is excluded by the expanded proviso b. However, it renders obvious the homolog compound where the two extra methyls appears on the methylene, i.e. -$(C(CH_3)_2)$-cyclopropyl. Such a homolog compound is structurally obvious for reasons set forth above. In addition, the reference itself provides a motivation for this exact alteration. Table 6 deals with R1=cyclopropyl compounds, and this exact modification is shown. Note that compound 54 has the R2= -(CH_2)-cyclopropyl and compound 60 has the -$(CHCH_3)$)-cyclopropyl. Compound 60 is twice as potent, which will motivate one of ordinary skill in the art to put an extra methyl --- or two extra methyl groups on that exact position in compound 80, as this teaching arises specifically in the context of R1=cyclopropyl compounds. In addition, the expanded proviso b does not bar the compound R1=cyclopropyl, R2= -(CH_2)-cyclopropyl(CH_3), i.e. the compound where a methyl group is attached to the cyclopropyl. Note that the cycloalkylalkyl choice permits substitution by methyl. In addition, the R2= -(CH_2)-cyclopropyl compound would render obvious the R2= -$(CH_2)_3$-cyclopropyl (i.e. cyclopropylpropyl) as a chain homolog. Note the

previously cited *Ex parte Ruddy*, 121 USPQ 427 has a C_3 link unpatentable over a C_1 link, and *Ex parte Nathan*, 121 USPQ 349 which found the insertion of a C_2H_4 link obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 6-36, 60-61, 68, 70, 72-73, 80-81, 83-96, 98-99 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48, 60-66, 78-79, 86-101, 107-118 of copending Application No. 10636996. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no line of demarcation between the two cases.

There is no patentable distinction between the two. Such a variation is considered obvious because of the close structural similarity. See *In re Hoeksema*, 154 USPQ 169; *Ex parte Weston*, 121 USPQ 428; *Ex parte Bluestone*, 135 USPQ 199; *In re Doebel*, 174 USPQ 158. As was stated directly in THE GENERAL TIRE & RUBBER COMPANY v. JEFFERSON CHEMICAL COMPANY, INC., 182 USPQ 70 (1974): "If any structural change is obvious to one skilled in the art, a substitution of the next higher homolog would seem to be." Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Applicants allege a lack of literal overlap. There is no requirement in law that claims must overlap for an Obviousness-type Double Patenting rejection; they must only be patentably distinct. Any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination, which does not require overlap. See *EX parte BLOCH*, 132 USPQ 207, *In re*

Borcherdt, 94 USPQ 175, *In re DOLL*, 82 USPQ 188, and *In re JENNINGS*, 77 USPQ 613, as examples of cases where overlap was not present.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 16-29, 33-34, 60-61, 68, 70-71, 80-81, 83-99 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The choice of "alkyl ether" for R2 is impossible. This is a molecule e.g. dimethylether, and hence has no valencies and cannot be a moiety. The traverse is unpersuasive. It is agreed that it "must have a valency" --- that is the examiner's point. Written as a molecule, it doesn't have one. Therefore it is not correct. As stated in In re Zletz, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous." Applicants state that what is actually

intended is the alkoxyalkyl group. Thus, that is the actual claim language which should be used.

2. The same is true for "hydroxamic acid, carboxamide" in the substituent list for aryl, heteroaryl and other places with aryl. The traverse is unpersuasive. There is no dispute as to what a hydroxamic acid is, it is a compound of the formula R–C(O)-NHOH (see the IUPAC definition in the "hydroxamic acids" reference. Applicants says "the hydroxamic acid substituent is the group –C(O)-NHOH". There is no basis for this assignment of valency to the carbonyl carbon. It could just as well be attached via the N, i.e. (RC(O))(OH)N-. It could be attached via the oxygen, i.e. –ONHC(O)R. Or it could be attached via a stem, i.e. –CH2CH2C(O)NHOH. Any of these three would be the moiety derived from a hydroxamic acid. If applicants intend C(O)-NHOH, they need to amend the claim accordingly.
3. The same is true for carboxamide, which is a compound having the structure $RC(=O)NR_2$. When used as a suffix in systematic name formation, it denotes the -$C(=O)NH_2$ group. If applicants intend -$C(=O)NH_2$, rather than e.g. -$C(=O)NR_2$, or $RC(=O)NR$-, then the claims should be amended accordingly.
4. The term "inflammatory arthritis" in claim 87 makes no sense. The word "arthritis" is simply a generic term for any inflammation of a joint arising from any cause and via any mechanism. That is, arthritis is inherently and always inflammatory, and hence the first word in this phrase makes no sense.
5. The starting material for the claim 71 should have a 2-CF_3 group, not 9-CF_3 group
6. The reference to "PDE4" in claims 85, 88 and 68 is unclear. The PDE4 family is encoded by four genes and thus there are actually 4 PDE4 types, PDE4A, PDE4B,

PDE4C, and PDE4D, and theses can occur in isoforms as well. These generally arise from the presence or absence of two unique N-terminal domains called upstream conserved regions 1 and 2 (UCR1 and 2), and other pieces which may be present. UCR1 and UCR2 have been shown to form a module necessary for the activation of PDE4 upon phosphorylation by the cAMP-dependent kinase (PKA). For example, there are at least 5 different forms of PDE4B: PDE4B1, PDE4B2 (the short form), PDE4B3, PDE4B4 and the very recently discovered PDE4B5. Distinct PDE4A isoforms include PDE4A1, PDE4A5, PDE4A4B, PDE4A7, PDE4A8, PDE4A10 and PDE4A11. PDE4D has 9 forms, 1-9. These various forms are not necessarily interchangeable, and there is substantial variation in distribution even within the subfamilies. Thus, PDE4A1 is abundant in the brain, PDE4A4B and PDE4A10 in inflammatory cells, PDE4A7 in brain and spleen, and PDE4A11 is very widely distributed. The PDE4D family is generally not seen in inflammatory cells as at all. Thus, PDE4D1 is seen in spleen and heart, PDE4D2 in the spleen, PDE4D3 in brains, lung and kidney, PDE4D4 and PDE4D6 in the brain, PDE4D5 in the lung and kidney, PDE4D7 in the brain and testes, PDE4D8 in the lung, heart and liver, and PDE4D9 in the spleen, heart and lung. Different types are regulated differently as well. ERK MAP kinases phosphorylate and regulate the activity of PDE4B, PDE4C and PDE4D but not PDE4A isoforms. It is reduced PDE4D activity which apparently causes defective RyR2-channel function associated with heart failure and arrhythmias. In dendritic cells (the cells responsible for the priming of naive T_h cells) it is predominantly PDE4A which is active, whereas monocytes mainly express PDE4B. It is the PDE4D5 isoform which preferentially interacts with the signalling scaffold proteins β-arrestin and RACK1. PDE4D3 likewise forms a signaling complex

with AKAPs such as AKAP450. The traverse is unpersuasive. While applicants state "Breadth is not indefiniteness", the examiner is not objecting to breadth per se. The problem is that there isn't a single thing called "phosphodiesterase 4" per se, only a collection of poorly understood enzymes. Applicants appear to assert that one of ordinary skill in the art would know how to determine whether a patient is "experiencing ... elevated phosphodiesterase 4" levels. How could this be done? What, for example is the normal level of PDE4B5 or PDE4D3 or PDE4A4? If the normal level is not known, how could one determine whether a patient is or is not suffereing from an elevated level?

7. The scope of claim 85's and 91's, "disease involving decreased cAMP levels", and similar language in claim 68 is unknown. Claim 54 cover both diseases which cause, and are caused by, decreased levels of cAMP. cAMP is a ubiquitous second messenger that controls a wide range of cellular events including movement, growth, metabolism, contraction, and synaptic plasticity. It does this by activation of PKAs, a family of kinases, EPAC proteins, by regulation of VEGF-induced endothelial cell cycle protein expression and activation of other agents which are still being investigated. cAMP production is regulated by many other agents, including PGE2, SDF-1/CXCL12, Gpa1, Nitric oxide, Ca2+, Angiotensin II, Dopamine, adrenomedullin, Hemin, melatonin, Urotensin II, GLP-1, Forskolin, TSH, PACAP, EP3, PI3Kgamma and many other hormones, nutrients, etc., so that inhibiting PDE4 will not always have any effect on cAMP. There is simply no way of knowing what the scope of the claims are.
8. Similarly, there is no way of knowing what the scope of claim 68 is. There are dozens of inflammatory disorders as are discussed below, but which ones result from depressed

cAMP or elevated PDE4 is unknown. There is no such list. The problem arises in part because PDE4 has such a wide range of effects. PDE4 as noted in the previous point, suppresses cAMP, and also norepinephrine. PDE4 regulates the L-type calcium current in human atrial myocytes, is involved in RyR2-channel function as noted above, is involved in chronic lymphocytic leukemia (CLL) apoptosis, regulates the signalling scaffold protein ß-arrestin. PDE4 appears to be a component of the NMDA receptor-mediated signal transduction pathway.

9. The inclusion of leukemia in claims 84, 87, 90, 93 makes no sense. This is not an inflammatory disorder.
10. Similarly, pyresis is not a disease state. It is a condition of elevated temperature, and may or may not be a symptom of disease.

Claims 68, 70, 75, 78, 81, 83-93, 98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the

content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the broad scope of R1 and R2, millions of compounds are covered. Claims 75, 78 are drawn to individual species and 91 to a list of species.

(b) Scope of the diseases covered.

I. For claim 85 and 91 as set forth above, it is entirely unclear which disease this would be, because there is only a limited understanding of the full role of cAMP in the body, and because of issues listed as 7 and 8 above. Note that this claim language covers diseases caused by decreased cAMP, as well as disease which themselves cause decreased cAMP.

II. Claims 84, 87, 90, 93 cover a subset of the diseases covered in the generic claims, discussed below in point IV. These claims cover both individual disorders, such as Behçet's disease and septic shock and SLE, and categories, such as "an inflammatory bowel disease" and "an autoimmune disease".

III. Claims 83, 86, 92 are drawn to two disorders, COPD and asthma.

IV. Claims 85, 88 and 68 cover inflammatory diseases which arise from decreased cAMP levels or elevated PDE4 levels or both. (It also covers allergic disease, but these are completely subsumed under inflammatory disease). As indicated above, there is no way of knowing which inflammatory diseases this does and does not cover, especially since PDE4 regulates, directly or via cAMP and various pro-inflammatory cytokines, so many different inflammatory practices. The analysis below assumes that it covers all.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Mechanistically, chronic inflammation encompasses a broad spectrum of immunologic processes, including antibody formation, antibody-dependent cell-mediated cytotoxicity, and cell-mediated immunity (delayed-type hypersensitivity). Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae.

Cystitis is any inflammation of the bladder, often caused by bacteria. Two ordinary types are eosinophilic and tuberculous cystitis. Interstitial cystitis (IC) is a particularly severe form, an inflammation of the bladder wall which may include Glomerulations. The origins and mechanism are largely unknown, and it isn't even clear whether there is just one form of the disease or several. There is no actual pharmaceutical treatment for the disease itself, although a few drugs can give some relief of symptoms, specifically Elmiron and DMSO.

Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

There is also a wide assortment of forms of conjunctivitis, including seasonal allergic conjunctivitis, perennial allergic conjunctivitis, giant papillary conjunctivitis (GPC) (a chronic yet poorly condition associated with contact lens wear), Vernal keratoconjunctivitis and atopic keratoconjunctivitis. In addition to types of allergic conjunctivitis there is also bacterial conjunctivitis (e.g. from Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus) and viral conjunctivitis (e.g. from gonorrhea, herpes simplex, chlamydia, adenoviruses or enteroviruses) Parasitic conjunctivitis (e.g. from *Onchocerca volvulus*, *Loa loa*, *Wuchereria bancrofti* or *Trichinella spiralis)*, fungal conjunctivitis (e.g. from *Candida albicans* or *Sporothrix schenckii)*, Phlyctenular Conjunctivitis, Inclusion Conjunctivitis, immunologic conjunctivitis, irritant conjunctivitis (e.g. from burns, chlorine or air pollutants), Radiation conjunctivitis, and assorted forms of neonatal conjunctivitis (which can be caused by e.g. a blocked tear duct).

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as

Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

The term "arthritis" is used for any kind of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF-I and IFN-K. It is thus an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long term obesity, but often the cause is unknown, and the full mechanism has not been discovered. It is treated with NSAIDs and COX-2 inhibitors. Complicating matters further is that fibromyalgia is sometimes also intended to be included in the loose term "arthritis". There is also Psoriatic Arthritis (including DIP, and spondylitis) which is believed to be autoimmune in origin but is a separate disorder from RA. There are also an assortment of infectious arthritis, i.e. arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses (or vaccinations given to

prevent viral infections), fungi, or parasites. Included in this category are various types of septic arthritis and mycotic arthritis, and viral arthritis, such as rubella arthritis, Lyme arthritis, Mumps arthritis, arboviral arthritis, syphilitic arthritis, parvovirus arthritis, tuberculous arthritis, Varicella arthritis, gonococcal arthritis, rubella arthritis, Reiter's syndrome (which includes a form of arthritis commonly arising from infection by Chlamydia trachomatis) etc. These assorted disorders can arise from quite varied sources. Thus, in addition to the above, CPDD, sometimes called pseudoosteoarthritis, or pseudogout, arises from Calcium Pyrophosphate Deposition. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine. Menopausal arthritis is due to ovarian hormonal deficiency. Neuropathic arthritis (which comes in several forms, such as Charcot's disease) can arise from sources as diverse as Diabetes Mellitus, Steroid treatment, Leprosy, Chronic alcoholism, Heavy metal poisoning and Neoplastic peripheral neuropathy. Arthritis can also arise from injury to the supporting ligaments or other structures contained within or associated with the joint, a condition often called post-traumatic arthritis.

Sinusitis is the inflammation of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis grown in the trapped secretions. In most cases it

requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and bacteria (Group A Beta Hemolytic Streptococci (GABHS), Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.

Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). The disease can be caused by fungi or viruses. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza.

Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Treatment may include antibiotics for bacterial pneumonia. Antibiotics may also speed recovery from mycoplasma pneumonia and some special cases. There is no clearly effective treatment for viral pneumonia.

Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment is purely supportive and may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual

obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.) Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to

remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is the inflammation of the meninges—the surrounding 3-layered membranes of the brain and spinal cord, and the fluid it is bathed in, (CSF). It can be caused by virtually any known infectious agent. Thus, if it is caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Myelitis is inflammation of the spinal cord.

Dactylitis is an inflammatory affection of the fingers.

Inclusion body myositis in an inflammatory slowly progressive proximal myopathy which may cause dysphagia and mild to moderate muscle wasting. Steroids and immunosuppression have generally been generally ineffective. Its pathogenesis is unknown, but ubiquitin, prion protein, and tau protein has been found in these inclusions.

Encephalitis is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Inflammation in the brain is a significant component of some important neurodegenerative conditions, including Alzheimer's Disease, AIDS dementia, Pick's Disease, Parkinson's Disease, and Huntington's Disease. The circumstances here are poorly understood because while there does not appear to be lympho-infiltrative processes, there is neuropathological evidence for immune activation. Thus, inflammation may be a disease-aggravating or even a disease-ameliorating factor in pathogenesis, or a non-contributory consequence of the injurious cascade of neurodegeneration and thus incidental.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis,

acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of

the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Another category of inflammatory disorders is Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis), a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. Some other types are idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

Many Occupational Lung Diseases are inflammatory in origin, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by

inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), aluminosis, anthracosis ("collier's lung", from the accumulation of carbon from inhaled smoke or coal dust in the lungs), chalicosis (stone-cutters' lung disease, due to inhaling stone dust), siderosis (occurring in iron workers, produced by the inhalation of particles of iron), tabacosis, hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings, and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Proctitis is a form of inflammation of the rectum, and includes Antibiotic-Induced Proctitis, Gonorrheal Proctitis, Herpetic Proctitis, Ischemic Proctitis, Radiation Proctitis, Syphilitic Proctitis and idiopathic proctitis.

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop into pulmonary fibrosis. Bronchiectasis, a lung disease in which pockets form in the air tubes of the lung and become sites for infection, can also occur. Treatment may include the use of corticosteroids.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics,

immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions. Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is a type of inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine. Vogt-Koyanagi-Harada syndrome (Harada's disease) is an acute inflammatory, immune-mediated disorder that can cause choroidal neovascularization, severe chorioretinal atrophy, and secondary glaucoma.

River blindness arises from inflammation of the eye caused by larvae (microfilaria) of the nematode *Onchocerca volvulus*, although the *Wolbachia* bacteria may be involved as well.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the

coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obli¢terans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilica¢lis, and verminous mesenteric arteritis.

Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal. The

basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in our lungs to become very thick and hard to remove. The high risk of infection in the respiratory system leads to damage in the lungs, lung that do not work properly, and eventually death of the cells in the lungs. The most common causes for infection in the lungs are Staphylococcus aureus, Haemophilus influenza and Pseudomonas aeruginosa (PA). The disorder itself is largely untreatable.

Osgood-Schlatter disease is a common form of inflammation of the knee in active adolescents. It has no pharmaceutical treatment per se. Other inflammations of the knee include Sinding-Larsen-Johansson disease, Patellofemoral syndrome, and osteochondritis dissecans.

Adhesive capsulitis is a type of inflammation of the shoulder. Its origin is usually unknown.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation.

It must be noted that an inflammatory response is a normal body process and for good reason. A certain level of inflammatory response is needed to protect the body from invading organisms, especially bacteria, viruses, and parasites. An acute inflammatory response is needed to activate the healing process for burns, mediated by a range of MMPs. In sprains or other ligament injuries, some inflammatory response is needed initially to initiate repair of the damage. In mechanical wounds, some inflammatory response is required for satisfactory wound healing and indeed anti-inflammatory drugs such as

cortisone can impair healing when administered at the time of wounding. In fact, inflammation is too important to be dependent on a single pathway and so inflammation can be initiated by numerous different systems, and generally, if one fails or is thwarted, another can do some or all of the job.

Note that many other disorders have been suggested as being directly related to PDE4, such as non-insulin dependent diabetes, Leishmaniasis, depression and dementia to name just some.

(2) The nature of the invention and predictability in the art: The invention is directed toward the treatment of disease and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage information that is provided on page 50 is generic, that is, it is not linked to any specific disease.

(4) State of the Prior Art: The prior art has established that there is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, histamine, fibrin, some PDE4 isoenzymes, kallikrein, plasmin, thrombin, PAF, Mac-1, VLA-4, VLA-5, VLA-6, VCAM-1, LFA-1, ICAM-1, Prostaglandins and cyclic endoperoxides (particularly prostacycline, prostaglandin E2, and thromboxane A2), leukotrienes (especially LTB4, LTC4, LTD4, and LTE4) and cytokines, and many, others. Examples of pro-inflammatory cytokines include IL-1I, IL-1ϑ, IL-6, IL-8, IL-18, MIP-1a, IFN-K and TNF-I. The Complement Pathway, which exists in two separate branches, uses C1, C4a,

C4b, C2, C3a, C3b, C5a, C5b, C6, C7, C8 and C9, as well as the membrane attack complex (MAC) and other complexes, C3 and C5 convertase enzymes, Magnesium ions, and Factors B, D, F, H, etc.

The prior art knows that mediation of inflammation is among the most pervasive and complex of all body process. There are complex interactions among just the cytokines, and just in certain types of inflammatory responses. As a second example, the Hageman factor is a protein that initiates three different processes: a) the intrinsic clotting process which operates via thrombin and fibrin, b) the fibrinolytic system which produces fibrinolysis via plasmin and 3) the kallikrein/kinin cascade, which produces the kinins, e.g. bradykinin. Further, Plasmin can also activate C3 and C5 in the complement cascade (an entirely separate set of vascular events) producing C3a and C5a, respectively, as can thrombin.

Further, the prior art knows that there are many paradoxical features in the inflammation system. As an example, in lung inflammation, nitric oxide appears to be a pro-inflammatory mediator in acute situations e.g. ARDS but anti-inflammatory in more stable situations. As a second example, the cytokine TGF-beta-1 possesses both pro-inflammatory and anti-inflammatory activities. Virtually all cells have TGF-beta-1 receptors, and the cytokine has many other roles other than in inflammation. As a third example, CRF appears to have both pro-inflammatory and anti-inflammatory activities.

Thus, the prior art knows that, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

These compounds are trifluoromethyl purines with a particular substitution pattern in 2 positions. So far as the examiner is aware, no polyfluoro-alkyl purines of any kind are in use for such disorders.

(5) Working Examples: There are no working examples of treatment of any disorder at all. Indeed, no specific biological data is presented for any specific compound.

(6) Skill of those in the art: For a compound or genus to be effective against inflammation generally is contrary to the present understanding of medical science. It establishes that it is not reasonable for any agent to be able to treat inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found. In terms of the individual inflammatory disorders, this is completely varied. It ranges from areas where the skill level is high, as in asthma, to ARDS, where the skill level is so low that there is no effective pharmacological treatment. In this regard, it is noted that claims 84, 87, 90, 93, 83, 86, and 92 include COPD. Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air

passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself. The examiner notes that extensive efforts have been made to try to get Ariflo® (cilomilast) and Daxas® (roflumilast) to be effective against COPD (and asthma) without, as of the present, success, evidence of the low skill level in this art. It is not known, of course, whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast.

(7) The quantity of experimentation needed: Owing to the factors listed above, especially in points 1, 4 5, and 6, experimentation needed will be extensive. Because of the sheer scope of this claim language, dozens of unrelated diseases will have to be tested. Many of these are already known to be resistant to pharmacological treatment as noted above.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Applicants state, " Applicants have cited numerous references that demonstrate that the use of PDE 4 inhibitors for treating inflammation is extremely well known in the art." A vague wave at the collection of references is not

sufficient. No reference states that PDE4 inhibitors are expected to be effective for the treatment of inflammatory disorders associated with decreased cyclic AMP levels or elevated PDE4 levels generally.

Indeed, the Martin the reference is actually a pretty strong argument against enablement, at least as of 2001. The paper, which does not report original research, couches it statement in general terms, e.g. "It is generally believed that inhibitors of PDE4 may have a useful bronchodilatory and anti-inflammatory actions." That type of wording indicates that such was not considered enabled. The paper notes that Ariflo ® is "predicted to be launched by the end of 2000 or early 2001", and mention. But, as noted above, cilomilast and roflumilast, two of the most extensively tested PDE4 inhibitors are, at present, not approved for the treatment of any disorder.

In fact, the notion that PDE4 inhibitors could treat such inflammation generally is contrary to what is already known about PDE4 inhibitors. To begin with, assorted PDE4 inhibitors have been shown to cause vasculitis (vasculitis is inflammation of blood vessels), and indeed, this has hindered clinical investigation of PDE4 inhibitors. For example, development of SCH-351591 was halted because of acute and chronic vasculitis in small to medium sized arteries, and vasculitis was found to be a significant problem with CI-1018 and Ariflo (cilomilast). The examiner must note that one of the diseases specifically named is Behçet's Disease, which is primarily characterized by vasculitis.

Nor is the problem limited to vasculitis. The PDE4 inhibitor IC542 was shown to trigger a generalized inflammatory response affecting the gastrointestinal tract, nearby mesentery, and thymus.

Applicants state, "Thus, an assertion that PDE4 inhibitors are not presently approved by the FDA for treating a given inflammatory disease does not establish any reason to doubt that PDE4 inhibitors can be used to treat that inflammatory disease, especially when the art recognizes that PDE4 inhibitors can be used to treat that inflammatory disease." This is not agreed with. The failure, as of the filing date and even as of the present, establishes that the skill level in this art is low relative to the difficulty of task, since a great deal of effort has not brought forth success. The assertion that "the art recognizes that PDE4 inhibitors can be used to treat that inflammatory disease" is not backed by any specific evidence. What the art indicates is that such use is worth investigating. This is particularly true for the specific diseases listed. For example, applicants are asked to point to which reference states that PDE4 inhibitors would be expected to be, or are, effective in treating Behçet's Disease or septic shock.

The examiner must point out moreover that applicants have included some disorders which are well known to be exceptionally difficult to treat, such as ADRS, septic shock, SLE, multiple sclerosis and cystic fibrosis.

Applicants state, "compliance with the enablement requirement of 35 U.S.C. 1 12, first paragraph, does not turn on whether an example is disclosed." The examiner has not said that it does. However, the absence of any working examples of treatment of any disorder and any specific biological data is one of the specific factors to be considered, as is set forth by *In re Wands*.

With regard to dosages, applicants point to pages 53-59 and examples 13-15. Page 53-59 have only synthesis data, and there are no examples 13-15. The dosage information actually appears on page 50, and is totally generic, so that it covers such unrelated

disorders as depression, Alzheimer's Disease, B cell chronic lymphocytic leukemia, septic shock, asthma, neurodegeneration arising from stroke and drug addiction.

Claim Objections

Claim 74 and 77 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 84, 87, 90, 93, third from last line should be spelled "Behçet's".

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Berch
Primary Examiner
Art Unit 1624

7/5/06